

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
 TRANSMITTAL OF COPY OF INTERNATIONAL
 PRELIMINARY REPORT ON PATENTABILITY
 (CHAPTER I OF THE PATENT COOPERATION
 TREATY)
 (PCT Rule 44bis.1(c))

Date of mailing (day/month/year) 14 June 2007 (14.06.2007)

To:

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 ETATS-UNIS D'AMERIQUE

Applicant's or agent's file reference NEREUS.079VP	IMPORTANT NOTICE	
International application No. PCT/US2005/044091	International filing date (day/month/year) 02 December 2005 (02.12.2005)	Priority date (day/month/year) 03 December 2004 (03.12.2004)
Applicant NEREUS PHARMACEUTICALS, INC. et al		

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Athina Nickitas-Etienne
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference NEREUS.079VP	FOR FURTHER ACTION See item 4 below	
International application No. PCT/US2005/044091	International filing date (day/month/year) 02 December 2005 (02.12.2005)	Priority date (day/month/year) 03 December 2004 (03.12.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant NEREUS PHARMACEUTICALS, INC.		

<ol style="list-style-type: none"> This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a). This REPORT consists of a total of 9 sheets, including this cover sheet. <p>In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.</p>																								
<ol style="list-style-type: none"> This report contains indications relating to the following items: <table> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. I</td> <td>Basis of the report</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table> 	<input checked="" type="checkbox"/>	Box No. I	Basis of the report	<input checked="" type="checkbox"/>	Box No. II	Priority	<input checked="" type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	<input checked="" type="checkbox"/>	Box No. IV	Lack of unity of invention	<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	<input checked="" type="checkbox"/>	Box No. VI	Certain documents cited	<input type="checkbox"/>	Box No. VII	Certain defects in the international application	<input checked="" type="checkbox"/>	Box No. VIII	Certain observations on the international application
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<ol style="list-style-type: none"> The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis.2). 																								

<table> <tr> <td>Date of issuance of this report 05 June 2007 (05.06.2007)</td> </tr> <tr> <td>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</td> </tr> <tr> <td>Facsimile No. +41 22 338 82 70</td> </tr> </table>		Date of issuance of this report 05 June 2007 (05.06.2007)	The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Facsimile No. +41 22 338 82 70
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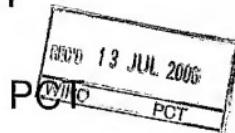
PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PTO/1



WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Applicant's or agent's file reference see form PCT/ISA/220		Date of mailing (day/month/year) see form PCT/ISA/210 (second sheet) FOR FURTHER ACTION See paragraph 2 below
International application No. PCT/US2005/044091	International filing date (day/month/year) 02.12.2005	Priority date (day/month/year) 03.12.2004
International Patent Classification (IPC) or both national classification and IPC INV. A61K31/407 A61P35/00		
Applicant NEREUS PHARMACEUTICALS, INC.		

1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx. 523656 epmu d Fax: +49 89 2399 - 4465	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Steendijk, M Telephone No. +49 89 2399-8460
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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/044091

Box No. I Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of:
 the international application in the language in which it was filed
 a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 a sequence listing
 table(s) related to the sequence listing
 - b. format of material:
 on paper
 in electronic form
 - c. time of filing/furnishing:
 contained in the international application as filed.
 filed together with the international application in electronic form.
 furnished subsequently to this Authority for the purposes of search.
3. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/044091

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

- the entire international application
 claims Nos. 12-22,41-85

because:

- the said international application, or the said claims Nos. 12-22,41-85 relate to the following subject matter which does not require an international search (*specify*):
see separate sheet
- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):
- no international search report has been established for the whole application or for said claims Nos.
- a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
 furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).
- a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.
- the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- See Supplemental Box for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/044091

Box No. IV Lack of unity of invention

1. In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
 - paid additional fees
 - paid additional fees under protest and, where applicable, the protest fee
 - paid additional fees under protest but the applicable protest fee was not paid
 - not paid additional fees
2. This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
 - complied with
 - not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
 - all parts.
 - the parts relating to claims Nos.

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, Inventive step or
Industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims	1-22,28,46,59-85
	No:	Claims	23-27,29-45,47-58
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-85
Industrial applicability (IA)	Yes:	Claims	1-11,23-41
	No:	Claims	

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2005/044091

- 1) The present application relates to the use of salinosporamides in treatment of drug resistant cancer (claims 1-22), of disease characterized by excessive / inappropriate angiogenesis (claims 23-58), Gleevec resistant cancer (claims 59-72), as well as of specific, alternatively fused salinosporamides for treatment of cancer (claims 72-85, see also claims 6, 17, 28, 46 and 64).
- 2) Cited documents
D1: WO 2004/071382 A
D2: WO 2004/043374 A)
D3: WO 96/32105
D4: LEUKEMIA RESEARCH, vol. 28, (2004-05), pages 39-45
D5: AM. J. CLIN. PATH., .vol. 116, no. 5, (2001-11), pages 637-646
D6: WO 2005/002572 A (2005-01-13)
D7: J.ORG.CHEM., no. 16,(2005-07-01), pages 6196-6203,
D8: WO 2006/028525 A (2006-03-16)

Documents D6-D8 were published after the claimed priority and are herein not considered as prior art.

- 3) Novelty
Document D1 describes various salinosporamides (not the alternatively fused compounds of claims 6, 17, 28, 46, 64 and 72-85) as proteasome inhibitors useful in the treatment of a variety of disorders, including cancer and angiogenic disease (see pages 19-20). This document does not disclose treatment of resistant cancer. In view of D1 claims 23-27, 29-45, 47-58 are not considered new.

Document D2 describes the use of proteasome inhibitors for treatment of resistant cancer cells, not however specifically of the defined salinosporamides.
Document D3 describes lactacystin analogues useful as proteasome inhibitors; the compounds of D3 lack the substitution "R3" in the compounds presently defined.
Document D4 describes the proposed use of proteasome inhibitors for treatment of Gleevec (imatinib) resistant cancer, not specifically of the defined salinosporamides.
Document D5 describes a variety of applications of proteasome inhibitors, including cancer treatment and as antiangiogenesis agent, however, not specifically of the

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2005/044091

(disease characterized by excessive / inappropriate angiogenesis in general or particular cancer types).